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(54) Title: HERBAL PREPARATION FOR MANAGEMENT OF CARDIOVASCULAR AND NEUROLOGIC DISORDERS

(57) Abstract: A herbal preparation for management of cardiovascular and neurologic disorders comprising at least two of the following constituents, and preferably all three: 1. *Dioscorea bulbifera*, 2. *Hippophae rhamnoides*, 3. *Bacopa monnieri* and present in the range of: 1. *Dioscorea bulbifera* 200-500 mg, 2. *Hippophae rhamnoides* 150-400 mg, 3. *Bacopa monnieri* 100-500 mg for every 1000 mg of said preparation.

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TITLE OF INVENTION

Herbal preparation for management of cardiovascular and neurologic disorders

FIELD OF INVENTION

5 This invention relates to a herbal preparation for management of cardiovascular and neurologic disorders and to a process for the preparation thereof.

10 The preparation of the present invention slows down the atherosclerotic changes and hence helpful in delaying the onset of hypertension among potential hypertension cases. The preparation also delays the development of frank diabetes mellitus and also slows down the early cognitive decline and neurologic disorders among likely patients.

15 The preparation is also helpful in increasing the general body resistance against physical and mental stress. It helps in neurophysiological adaption following cold stress. Such a preparation also prevents the individual from pneumonia following cold exposure.

BACKGROUND OF INVENTION

20 Ageing is a normal physiological phenomena resulting from intrinsic and extrinsic damage to the various organs particularly cardiovascular and neurologic system. The magnitude of ageing process depends upon genetic as well as environmental factors. A wide variety of disorders appear among the ageds.

25 Rapid atherosclerotic changes results in cerebrovascular accidents and ischaemic heart disease similarly due to brain ageing cognitive decline and other cognitive deficit disorders are common among the ageds. Dementia of Alzheimer's type is one of the important cause of motility and morbidity

among the ageds. Dementia of Alzheimer's type is one of the important cause of motility and morbidity among the aged population.

The currently available drugs have shown tremendous side effect and has no preventive role in age related disorders.

5 **OBJECTS OF THE INVENTION**

The main object of this preparation is to propose a novel preparation for the prevention of rapid atherosclerotic changes among the individuals showing evidence of potential hypertension.

10 Another object of this invention is propose a herbal preparation to delay the onset of frank diabetes.

Still another object of this invention is to propose a novel preparation for increasing general body immunity among those persons who have low body resistance.

15 Yet another object of this invention is to propose a novel preparation to prevent the cognitive decline among ageds.

Another object of this invention is to propose a herbal preparation to regulate abnormal lipid profile particularly LDL-c and triglycerides to prevent blockage of coronary, artery and vessels of brain.

DETAILED DESCRIPTION OF INVENTION

20 According to this invention there is provided a herbal preparation for management of cardiovascular and neurologic disorders comprising at least two of the following constituents, and preferably all three:

1. *Dioscorea bulbifera*
2. *Hippophae rhamnoides*
3. *Bacopa monnieri*

and present in the range of:

1. <i>Dioscorea bulbifera</i>	200-500 mg
2. <i>Hippophae rhamnoides</i>	150-400 mg
3. <i>Bacopa monnieri</i>	100-500 mg

for every 1000 mg of said preparation.

The preparation may also comprise known additives such as minerals, vitamins, salts, fillers (for encapsulation) and binders, if required and present in trace amounts.

1. <i>Dioscorea bulbifera</i>	200-500 mg
2. <i>Hippophae rhamnoides</i>	150-400 mg
3. <i>Bacopa monnieri</i>	100-500 mg

15 Thus, any known additive or supplement is added to prepare the final capsule if required, and present in trace amounts. Reference is made herein to a capsule. However, it would be apparent that the preparation may also be in the form of a tablet.

Preferably, the preparation comprises:

20	1. <i>Dioscorea bulbifera</i>	200-300 mg
	2. <i>Hippophae rhamnoide</i>	250-350 mg
	3. <i>Bacopa monnieri</i>	250-500 mg

for every 1000 mg of the preparation.

Dioscorea bulbifera:

Dioscorea bulbifera belongs to the family of Dioscoreaceae, it is a creeping plant with a bulbous root. The plant is a climber. The tuberous bulb is about two to four inches in diameter and brown in colour. The leaves and stem of the plant contains toxic alkaloids but the tuberous part of the plant mainly contains the terpenoidal glycosides. The remaining part of the bulb contains starch, calcium oxalate.

Hippophae rhamnoides

Hippophae rhamnoides commonly known as Seabuckthron is a small genus of shrubs and trees and is native of temperate region. It belongs to family elaeagnaceae. Fruits and leaves are commonly used for medicinal purpose. The fruit residue is quite rich in protein, fats, amino acids. The ripe fruits contain many type of vitamins. The stem contains SHT the rare occurrence in the plant kingdom.

Bacopa monnieri

Bacopa monnieri is commonly known as Brahmi is an annual creeping plant found throughout India in wet, damp and marshy areas. In Ayurvedic medicine this plant is used as a nervine tonic in the management of mental sub-normalcy, instability and epilepsy. Total plant is used for the medicine purposes. The plant contains crystalline compound and its one of the components crosses the blood brain barrier.

Example 1

The preparation containing the organic extract of *Dioscorea bulbifera* was given in the dose of 100-150 mg per day did not show any action on circadian blood pressure. Similarly in this dose no alteration was observed in the level of post prandial glucose level. The effective dose varies from 200-500 mg per day. The single drug therapy significantly slow downs the process of atherosclerosis in experimental animals.

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Example 2

When the organic extract of *Dioscorea bulbifera* administered in the dose of 200-300 mg per day along with the organic-extract of fruits of *Hippophae rhamnoide* in the dose of 200-300 mg improvement was noticed in the variation of systolic and diastolic blood pressure following circadian blood pressure changes. Similarly when the organic extract of *Dioscorea bulbifera* alongwith *Hippophae rhamnoide* was given in the dose of 200-300 mg per day and 150 to 400 mg per day a 1 reduction in the level of systolic and diastolic blood pressure was observed following cold pressor test.

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The post prandial blood glucose level also showed significant reduction in this particular range of combined effect of two drugs in relation placebo group.

Example 3

When the organic extract of *Bacopa monnieri* in the dose of 100 mg to 200 mg per day alongwith the organic extract of *Hippophae rhamnoide* was administered 200-300 mg per day and *Dioscorea bulbifera* in the dose of 150-200 mg per day a considerable improvement was noticed in general feeling of well being, better sleep and good appetite. The subjects also

showed better tolerance to heat and cold. The subject developed better neurophysiological adaptation following stress.

Example 4

When the organic extract of *Dioscorea bulbifera* was given in the dose of 200-300 mg per day alongwith the *Hippophae rhamnoide* in the dose of 200-350 mg per day alongwith the organic extract of *Bacopa monnieri* in the dose of 250-400 mg per day presented good results in the form of significant reduction in the cardiovascular reactivity and arrest the rapid decline of the cognitive function.

Example 5

In this series when the organic extract of *Dioscorea bulbifera* in the dose of 200-300 mg per day alongwith organic extract of *Hippophae rhamnoide* in the dose of 250-350 mg and *Bacopa monnieri* in the dose of 250-400 mg per day was administered simultaneously twice in a day the subject reported good sleep and reduced systolic and diastolic blood pressure. The cardiovascular recording was also found reduced following cold stress. About 70 percent cases reported overall feeling of well-being.

Example 6

When the organic extract of *Hippophae rhamnoide* in the dose of 250 mg to 300 mg per day and the organic extract of *Bacopa monnieri* in the dose of 300 to 350 mg per day the individuals showed a better tolerance to frequent cold and cough, their body resistance towards diseases increased significantly and thus the occurrence of pneumonia also reduced following test drug treatment.

Example 7

The cases receiving the organic extract of *Dioscorea bulbifera* in the dose of 200 to 250 mg per day, *Hippophae rhamnoide* in the dose of 150 to 200 mg and *Bacopa monnieri* in the dose of 200 to 250 mg exhibited improvement in overall mental performance particularly improvement in attention and memory performance. An early fatigue which was a major complaint among the subjects, improved to a great extent and a better physical fitness was reported by the subjects.

Example 8

When the organic extract of *Dioscorea bulbifera* in the dose of 150 to 250 mg per day and *Bacopa monnieri* in the dose of 250 to 300 mg per day was administered, a significant reduction in hyperexcitability, aggressive behaviour, anxiety and stress including depressive behaviour improved among the test drug treated group. A regulated improved behaviour exhibited the beneficial role of this combination.

Process of extraction

The tuberous part of the *Dioscorea bulbifera* was properly washed and shed dried. After cutting in pieces the tuber were initially extracted with alcohol at 60 to 70c for 70 hrs. The solvent was recovered at same temperature on single distillation set of 90% concentration. The organic extract was further separated by column chromatography method to obtain crystals. The chemical characterization of the crystal was made by HPTLC and spectroscopic method. After chemical characterization, the extracted material was subjected to experimental study for the evaluation of the therapeutic potential of the extracted materials. The total extracted material

was kept between 20 to 30C. The biological activity of the plant material can only be sustained on this temperature.

Similarly the drug fruit of dry fruits of Hippophae rhamnoide was initially extracted with alcohol at the temperature 60 to 70C continuously for 70 5 hours. The aqueous fraction was also obtained by using buchhi vacuum rotatory apparatus at low temperature.

Shed dried total plant of the Bacopa monnieri was extracted in alcohol at the temperature of 60 to 70C to obtain extract. Further extract was treated with column chromatography to obtain the crystals. The chemical 10 characterization of crystal was done by HPTLC and spectroscopic methods.

The extract in the crystalline form was subjected to animal study for safety and efficacy profile. The whole process was performed on a particular temperature in order to obtain various chemical constituents responsible for the therapeutic efficacy. The therapeutic efficacy can only be obtained if all 15 the chemical constituents are mixed for oral consumption.

It was found that when the organic extract of Dioscorea bulbifera alongwith the organic extract of Hippophea rhamnoide was given in the doses described continuously for long period the subject showed marked reduction in the level of systolic and diastolic blood pressure following cold pressure following cold pressure test. The average variation in the level of circadian 20 blood pressure also reduced. Thus in potential hypertensive cases the early onset of Hypertension can be minimized after oral administration of this formulation. Thus the anti atherosclerotic property is proved by the oral administration of above formulation.

When the organic extract of *Dioscorea bulbifera* along with extract of dry fruits of *Hippophae rhamnoide* was given to subjects hereinabove, a mark reduction in the post prandial blood sugar level was observed. It indicates that the combined effect of *Dioscorea bulbifera* and *Hippophae rhamnoide* played a preventive role in the development of frank diabetes in the susceptible cases.

When organic extract of *Bacopa monnieri* particularly different glycoside fraction alongwith the organic extract of *Dioscorea bulbifera* was given (*Dioscorea bulbifera* 150 to 300 mg, *Bacopa monnieri* 150 to 450 mg), a considerable improvement was noticed in the reduction of cognitive decline alongwith the stabilization of systolic and diastolic blood pressure. In this particular dose the drug is beneficial in the management of senile dementia.

When the extract of *Dioscorea bulbifera* 200 to 300 mg, *Hippophae rhamnoide* 250 to 350 mg, *Bacopa monnieri* 150 to 300 mg was administered only 60 percent cases reported general feeling of well being, reduction in anxiety level and reduction in cardiovascular reactivity following cold stress. About 10 percent reduction in body weight was reported among obese individuals.

When the extract of *Dioscorea bulbifera* 250-500 mg, *Hippophae rhamnoide* 300 to 500 mg, *Bacopa monnieri* 250 to 450 mg was given, the 78 percent cases reported general feeling of well being, reduction in anxiety level 72 percent cases reported reduction in cardio vascular reactivity particularly in the form of systolic and diastolic blood pressure.

A considerable improvement was noticed in the adaptation pattern against physical and mental stress. The 15 percent reduction in total body weight was observed.

WE CLAIM:

1. A herbal preparation for management of cardiovascular and neurologic disorders comprising at least two of the following constituents, and preferably all three:

5 1. *Dioscorea bulbifera*
 2. *Hippophae rhamnoides*
 3. *Bacopa monnieri*

and present in the range of :

10 1. *Dioscorea bulbifera* 200-500 mg
 2. *Hippophae rhamnoides* 150-400 mg
 3. *Bacopa monnieri* 100-500 mg
for every 1000 mg of said preparation.

2. A herbal preparation as claimed in claim 1 comprising:

15 1. *Dioscorea bulbifera* 200-300 mg
 2. *Hippophae rhamnoides* 250-350 mg
 3. *Bacopa monnieri* 250-500 mg

for every 1000 mg of said preparation.

3. The herbal preparation as claimed in claim 1 comprising known additives such as minerals, vitamins, salt, fillers and/or binders.

20 4. The herbal preparation as claimed in claim 1 comprising organic solvents of *Dioscorea bulbifera*, *Hippophae rhamnoides*, and *Bacopa monnieri*.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 02/00233

CLASSIFICATION OF SUBJECT MATTER		
IPC ⁷ : A61K 35/8		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
IPC ⁷ : A61K 35/78		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
WPI, EPODOC, MEDLINE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.		<input checked="" type="checkbox"/> See patent family annex.
<small>* Special categories of cited documents: „A“ document defining the general state of the art which is not considered to be of particular relevance „E“ earlier application or patent but published on or after the international filing date „L“ document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) „O“ document referring to an oral disclosure, use, exhibition or other means „P“ document published prior to the international filing date but later than the priority date claimed</small>		<small>„T“ later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention „X“ document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone „Y“ document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art „&“ document member of the same patent family</small>
Date of the actual completion of the international search 5 June 2003 (05.06.2003)		Date of mailing of the international search report 3 July 2003 (03.07.2003)
Name and mailing address of the ISA/AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No. 1/53424/535		Authorized officer WOLF K. Telephone No. 1/53424/436

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International application No.

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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INTERNATIONAL SEARCH REPORT
Information on patent family members

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